JONES WALDO HOLBROOK & MCDONOUGH PC

ATTORNEYS & COUNSELORS
Est. 1875

TEL: 801-521-3200
FAX: 801-328-0537

170 SOUTH MAIN ST, SUITE 1500
SALT LAKE CITY, UTAH 84101

WWW.JONESWALDO.COM

FAX TRANSMISSION COVER SHEET

To: Examiner Melanie J. Yu
Group Art Unit: 1641

Commissioner for Patents

From: K. S. Cornaby

Number of Pages (including cover page) 11

Hard Copy to Follow: ☐ Yes ☒ No

DATE: 04/21/05

Fax No.: 571 273 8300

TIME: 8:00 a.m.

Phone No.: 571 272 2933

Client Name:

Charge No.: 13368.0001

Additional Information:

Re: U.S. Patent Application: 10/706,547
Powers et al.

IF YOU DID NOT RECEIVE ALL PAGES, PLEASE CALL (801) 521-3200, ext. 7361

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

APPLICANTS: LINDA S. POWERS, et al.

SERIAL NO.: 10/706,547

FILED: November 12, 2003

FOR: TAXONOMIC IDENTIFICATION OF PATHOGENIC MICROORGANISMS AND THEIR PROTEINS

GROUP ART UNIT: 1641

EXAMINER: MELANIE J. YU

RESPONSE

April 20, 2005

Mail Stop Amendment
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Sir:

In response to the Office Action mailed December 23, 2004, for which Applicants have filed a request for a one-month extension of time to 04/23/05 in which to respond, please see the following attached sheets.

The undersigned attorney expresses appreciation for the telephone conference he and the Applicant Christopher Lloyd had with Examiner Yu on 03/29/05.

Respectfully submitted,

K. S. Cornaby
Attorney for Applicants
Jones Waldo Holbrook & McDonough PC
170 South Main Street, Suite 1500
Salt Lake City, UT 84101
(801) 521-3200

CERTIFICATE OF FACSIMILE TRANSMISSION

I hereby certify that the attached Response is being facsimile-transmitted to Examiner Melanie J. Yu, Commissioner for Patents, Washington, D.C. fax (571) 273-8300 on the 22nd day of April, 2005.

Roberta M. Kelly

STATEMENT OF THE SUBSTANCE OF THE INTERVIEW

Applicant argued that Hudson teaches an HPMP, and does not teach covalently tethered ligands. However, Examiner relies upon Hudson for the step of separating bound analyte from non-binding components, and does not rely upon Hudson for linkers bound to a photostable linker. Applicant also argued that Powers does not teach a photostable linker, but the linkers exemplified in Powers are the same as the photostable linkers exemplified in the instant application. Therefore the linkers taught by Powers would inherently be photostable.

All participants (applicant, applicant's representative, PTO personnel) should be corrected as follows:

1. Melanie Yu
2. Long Le
3. Christopher Lloyd
4. K. S. Cornaby

RESPONSE

In response to the Examiner's rejection of claims 21-23, 26 and 53 as being unpatentable over Powers, et al., in view of Hudson, et al., Applicants respond as follows:

Powers et al. (WO 98/49557) does teach a method for the identification of a biological analyte comprising (pg. 25, first paragraph): (a) exposing a solution containing the analyte to a ligand specific for the analyte of interest that has been tethered to a sensor chip surface, and (b) subjecting the ligand-tethered substrate surface with electromagnetic radiation to detect analyte binding via ratio fluorescence (copending application 659,043). (Powers et al. does not teach the use of photostable linkers; the instant application teaches, "It is important to note that the tether should not be photocleavable or otherwise chemically labile in the solution used to wash the ligand-tethered surface." (pg. 11, paragraph 2 – also mentioned on pg. 8, paragraph 1).)

Both Powers et al. and the instant application use identical chemistries as illustrative examples of how to tether ligands to substrate surfaces. However, both Powers et al. (pg. 19, paragraph 2) and the instant application (pg. 20, paragraph 2) teach, "The various ligands are preferably tethered to a substrate by means of organic coupling agents which are themselves known to those skilled in the art." The instant application goes further (pg. 21, last paragraph – pg. 22, first paragraph) when it states, "The chemical reactions used in tethering ligands to the surface of the sensor chip are known to those skilled in the art and are described in the literature. Such reactions may be found in G. T. Hermanson Bioconjugate Techniques (San Diego: Academic Press, 1966); Hansson et al., "Carbohydrate-Specific Adhesion of Bacteria to Thin Layer Chromatograms: A Rationalized Approach to the Study of Host Cell Glycolipid Receptors" (Analytical Biochemistry 146: 158-163 (1985)); and, Nilsson et al., "A Carbohydrate Biosensor

Surface for the Detection of Uropathogenic Bacteria" (Bio/Technology 12: 1376-1378 (December 1994))." Powers et al. further teaches (pg. 23, paragraph 2), "As will be appreciated by those skilled in the art, many other techniques can likewise be used to tether an appropriate ligand to the surface..." Similarities between the tethering chemistries (which are known to those skilled in the art) in Powers et al. and the instant application are present, but it is important, however, to note the differences in what each specification teaches about the tethers themselves.

As cited by the examiner, Powers et al. does not teach the linker being covalently tethered to a substrate surface via a tether having a length of at least 6 Å. This is a ***notable*** difference between Powers et al. and the instant application, which teaches not only the required length of the tether, but the reason why the tether size is important (pg. 11, paragraph 2): "***Binding efficiency is dependent upon the length of the tether.*** Microbes are found to bind most efficiently to ligands that are around forty Å long. Ligands directed to microbes are covalently attached to the substrate surface by tethers that are at least fifteen Å in length; ligands directed to proteinaceous toxins are at least six Å long."

Hudson et al. teaches separating weak binding and excess analyte from bound analyte by physical separation (e.g., centrifugation Column 18, lines 1-24) or washing (Column 14, lines 37-42). However, the washing and/or physical separation taught by Hudson is for removal of weak binding components of the solution from the HPMP layer, not for the removal of non-binding components of a solution from a surface. The presence of the HPMP layer is fundamental to the invention of Hudson et al. The HPMP layer is disclosed as necessary to (1) overcome surface effects on tagged target molecule (TTM)-ligand interactions (col. 3, lines 5-8), (2) permit rapid diffusion of unbound

molecules from the HPMP matrix back into the bulk solvent (col. 3, lines 52-55), (3) provide a hydrated (solvent-like) environment for ligand binding (col. 2, lines 13-21), and (4) increase ligand densities (col. 4, lines 56-62). The introduction of the HPMP layer to the substrate surface provides a "tortured path" for the analyte solution and introduces a partition thereby increasing nonspecific adsorption.[1] (The HPMP layer, much like a gel or particles used in affinity chromatography, slows the flow of the TTM containing-solution thereby increasing residence time of the analyte in the vicinity of the ligand. This increase in exposure time of the TTM to the ligand improves binding kinetics.) It will be appreciated by those skilled in the art that any weak-binding or excess TTMs would still be dissolved in the solution contained in the HPMP; since the HPMP was designed to remain hydrated (col. 3, lines 52-55) the excess and weak-binding TTMs would remain in the HPMP and need to be removed before detection of the tags. Thus, one reading Hudson et al. would appreciate that removal of excess and weak-binding TTMs was occurring from the HPMP.

Additionally, Hudson et al. teaches that washing can remove signal arising from specifically bound material, stating (col. 16, lines 57-58), "The more extensive the washing the more signal is removed." However, Hudson et al. counsels against using surface-tethered peptide ligands (with consequential low aqueous solubility and detrimental surface interactions) as close to the surface as the present application teaches due to artifacts introduced by surface effects (col. 3, lines 5-8). Subsequently, having knowledge of Hudson et al., and of the negative impact washing would have on the strength of the signal arising from analyte-ligand binding that it teaches (especially when

[1] The effects of the matrix on soluble analytes are known to those reasonably skilled in the art. The partition process is discussed in detail on pp. 18 in "The Principles of Thin-Layer Chromatography" by Kurt Randerath (1963, Academic Press, New York). The equilibria between analyte and matrix are described on pp. 7-11 in "An Introduction to Chromatography on Impregnated Glass Fiber" by Frederick Haer (1968, Ann Arbor Science Publishers, Inc., SBN 87591-007-6).

the ligand is tethered to the substrate surface), it would be apparent that washing would be detrimental. Thus, one reading Hudson would be counseled to ***not*** use either the method of the instant application or of Powers et al.

Additionally, there is another important difference in why washing is used between Hudson et al. and the instant specification, with this additional difference arising from the differing applications of the technologies and methods. Hudson et al. teaches washing in order to reuse ligand-conjugated HPMP surfaces (Abstract and Column 8, lines 17-19), and for "removal of excess target and other molecules" (Column 3, lines 60-63). The instant application teaches (pg. 12, paragraph 3), "Physical separation and washing remove non-binding components of the solution." It can be appreciated by those skilled in the art that if "excess target" (i.e. more target in solution than surface-tethered ligands) were present in the method taught by the instant application, then quantitation of analyte (like that taught in Figure 1 of the instant application) would not be possible since ligand saturation would occur. Furthermore, the method taught by Hudson et al. is designed to provide "an environment substantially equivalent to natural aqueous solutions for affinity binding" (Column 3, lines 66-67), thus addressing ligand solubility issues (col. 3, lines 2-5), and target analyte elution considerations (col. 4, lines 63-65) that they teach would be present in the method described in the instant application. The method described by Hudson et al. thus allows weak affinity binding between analytes and ligands to be determined (col. 18, lines 1-9) by using excess target analyte. (Using an excess of target is both known and practiced by those skilled in the art in determining binding constants between ligands and biological analytes – see Chapter 2 of Winzonr D.J. & Sawyer, W.H. Quantitative Characterization of Ligand Binding (New York: Wiley-Liss, 1995).)

Hudson et al. teaches (Column 14, lines 34-38), "The winks [HPMP ligand-tethered surfaces] were suspended in [0.15 mL] of phosphate buffered saline, and various concentrations of ^{125}I-radiolabeled Streptavidin were added and *incubated for ca. 2 hours*. The winks were washed and counted on a gamma counter to determine binding saturation." The instant application teaches (pg. 3, paragraph 2), "Thus, there is clearly a need for rapid and inexpensive techniques to conduct field assays for toxic proteins and pathogenic microorganisms that plague animals as well as humans" and (pg. 6, paragraph 1), "In addition, such techniques require high sensitivity when less than 100 cells are present and analysis that can be completed in the field in *less than 15 minutes*." Thus, the differences in purpose between Hudson et al. (determination of solution-estimated equilibrium binding) and the instant application (rapid determination and quantitation of biological analytes) are illustrated.

Powers et al. (WO/49557) teach the biological analyte being proteinaceous toxins (pg. 1, 1st paragraph and pg. 10, 2nd paragraph) and the peptide specific for a proteinaceous toxin (pg. 13-14; pg. 25, 1st paragraph). However, Powers et al. does not teach the linker being covalently tethered to a substrate surface via a tether having a length of at least 6 Å, nor the separation of the bound analyte from non-binding components of the solution. The absence of instructions on the nature of the tether is a notable difference between Powers et al. and the instant application, which teaches not only the required length of the tether, but the reason why the tether size is important (pg. 11, paragraph 2): "Binding efficiency is dependent upon the length of the tether. Microbes are found to bind most efficiently to ligands that are around forty Å long. Ligands directed to microbes are covalently attached to the substrate surface by tethers

that are at least fifteen Å in length; ligands directed to proteinaceous toxins are at least six Å long."

As cited by the examiner, Powers et al. (WO 98/49557) teaches (pg. 31, last line – pg. 32, lines 1-3), "As will be appreciated by those skilled in the art, a variety of bacterial cell components or metabolites as well as proteins and peptides exhibit intrinsic fluorescence when illuminated by UV light." And though Table 2 of Powers et al. teaches excitation of Tryptophan (and to a lesser extent tyrosine) at 295 nm (encompassed within the instant specifications citation between 200 and 300 nm), the detected emission peak is cited as 305 nm (alternatively between 295 and 315 nm, not exclusively contained within the presently disclosed 300 – 400 nm range). It is also important to note that Powers et al. specifically teaches (pg. 33, paragraph 1), "Then, the fluorescence of the [analyte exposed ligand-conjugated] chip can be measured with the probe 16 for the purpose of detecting which of the sections of the sensor chip have analytes bonded thereto." The intrinsic fluorescence obtained by probe 16, obtained through the method taught specifically by Powers et al., is specifically ratio fluorescence. Powers et al. teaches the detection of analytes by ratio fluorescence in Figure 5, and further describes its necessity on pg. 31, paragraph 2 ("By comparing fluorescence signals to reflected signals, the system as described in detail in the foregoing, copending application, normalizes the signals. That allows the system to compensate for variations between different surfaces.")

Powers et al. does teach the use of intrinsic fluorescence for the detection of proteins, but others skilled in the art do as well (see U.S. Patents 5,474,910; 5,760,406; 5,968,766 and 6,750,006). And though Powers et al. teaches intrinsic fluorescence detection of proteins captured by a peptide ligand, it teaches neither the steps of

physically separating the ligand-coated surface, washing away non-bound portions of the sample (biological components of the matrix from which the analyte was captured) nor the indicated tether lengths that are to be used for each kind of biological analyte.

Though Hudson et al. teach a peptide ligand containing from two to about 100 amino acids (col. 7, line 64 – col. 8, line 11), which reads on the recited range of three to twenty amino acids of the instant application. However, Hudson et al. counsels against using surface-tethered peptide ligands (with consequential low aqueous solubility and detrimental surface interactions) as close to the surface as the present application teaches due to artifacts introduced by surface effects (col. 3, lines 5-8). Thus, one reading Hudson would be counseled to ***not*** use the method of the instant application.